Transcriptome Profiling of Patient-Specific Human iPSC-Cardiomyocytes Predicts Individual Drug Safety and Efficacy Responses In Vitro.

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Public Summary:

Scientific Abstract:
Understanding individual susceptibility to drug-induced cardiotoxicity is key to improving patient safety and preventing drug attrition. Human induced pluripotent stem cells (hiPSCs) enable the study of pharmacological and toxicological responses in patient-specific cardiomyocytes (CMs) and may serve as preclinical platforms for precision medicine. Transcriptome profiling in hiPSC-CMs from seven individuals lacking known cardiovascular disease-associated mutations and in three isogenic human heart tissue and hiPSC-CM pairs showed greater inter-patient variation than intra-patient variation, verifying that reprogramming and differentiation preserve patient-specific gene expression, particularly in metabolic and stress-response genes. Transcriptome-based toxicology analysis predicted and risk-stratified patient-specific susceptibility to cardiotoxicity, and functional assays in hiPSC-CMs using tacrolimus and rosiglitazone, drugs targeting pathways predicted to produce cardiotoxicity, validated inter-patient differential responses. CRISPR/Cas9-mediated pathway correction prevented drug-induced cardiotoxicity. Our data suggest that hiPSC-CMs can be used in vitro to predict and validate patient-specific drug safety and efficacy, potentially enabling future clinical approaches to precision medicine.